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Case Report

Dosing interval adjustment of denosumab for the treatment of giant cell tumor of the sphenoid bone: A case report

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ABSTRACT

Background: In the treatment of giant cell tumor of bone (GCTB), the efficacy and safety of denosumab, a receptor activator nuclear factor κ-B ligand inhibitor, has previously been demonstrated, especially for unresectable tumors. One of the current issues in denosumab treatment for unresectable GCTB is whether it can be discontinued, or whether the dosage or the dosing interval can safely be adjusted, if discontinuation is not possible, to avoid the occurrence of side effects.

Case Description: A 15-year-old boy with diplopia was referred to our hospital after a space-occupying lesion in the sphenoid bone was found on head CT. Partial removal of the tumor was performed through an endoscopic endonasal approach, and pathological diagnosis was confirmed as GCTB. Thereafter, the patient received 120 mg subcutaneous injections of denosumab every 28 days for the first 2 years. Since bone formation was induced and sustained along with tumor reduction, the dosing interval was gradually extended, with 4 monthly dosing for the next 1 year, followed by 6 monthly dosing for the succeeding 2 years. With the extension of the dosing interval, the ossified tumor has regrown slightly, but within an acceptable range.

Conclusion: Discontinuation of denosumab treatment for unresectable GCTB was not thought to be possible for the current case due to the nature of the drug, as reported in the literature. Extending the dosing interval up to 6 monthly, as could be done safely in the current case, can be considered a useful and appropriate measure.

Keywords: Denosumab, Dosing interval, Giant cell tumor of bone, Sphenoid bone

INTRODUCTION

Giant cell tumor of bone (GCTB) is an uncommon, osteolytic tumor that occurs mainly in young adults (peak incidence ages, 20–40 years) with a slight female predominance (3:2).[4,9,11] GCTB most commonly affects the epiphyses of long bones, particularly of the distal femur and proximal tibia.[4,16] Only a minority of patients present with tumors in the skull, mostly arising from sphenoid or temporal bones.[1,4] Although regarded as benign, GCTB can recur locally following even *en bloc* surgical resection.[15] Furthermore, hematogenous metastasis to the lung or malignant transformation may occur in some patients.[4,6,16]

Although a complete surgical removal with invaded bone is generally the gold standard of treatment for GCTB,[7,14,15] the surgical extent can often be limited due to proximity to vital structures, especially in skull base lesions. Therefore, establishment of adjuvant treatments and strategies is very important for the management of unresectable GCTB.[7] Since no promising adjuvant treatment for unresectable GCTB, including radiotherapy, embolization, or chemotherapy, has been established,[14-16] denosumab, a fully human monoclonal antibody that inhibits a receptor activator nuclear factor κ-B ligand (RANKL), has been introduced to the treatment of GCTB. The usefulness of denosumab has been demonstrated in the control of unresectable GCTB, through blocking the RANKL-RANK interaction between neoplastic mononuclear stromal cells and osteoclast-like giant cell precursors inhibiting their maturation and as a result bone resorption.[3,13] An issue that has arisen is the need to consider the possibility of discontinuation of the denosumab treatment, or adjustment of the dosage or dosing interval if discontinuation is impossible, to avoid the occurrence of adverse effects. We herein report a case of a patient with unresectable GCT in sphenoid bone, showing a good response to denosumab treatment, with tumor growth well controlled by the drug for 5 years, as the dosing interval was gradually adjusted.

Clinical presentation

Informed consent was obtained from the patient and his guardian. A 15-year-old boy presented with diplopia which had an insidious onset, progressing over a period of 2 months. He was referred to our hospital after a space-occupying lesion was pointed out in the sphenoid bone on computed tomography scan (CT) of the head by an area doctor. On admission, neurological examination revealed bilateral abducens nerve palsy. CT and magnetic resonance imaging (MRI) showed a well-enhanced mass lesion in the sphenoid sinus, with osteolytic invasion of ethmoid cells anteriorly, the sellar floor, dorsum sellae, and posterior clinoid processes posteriorly, and the clivus inferiorly [Figure 1]. For the purpose of confirmation of pathological diagnosis and maximum volume reduction, tumor removal was performed through an endoscopic endonasal approach. Portions invading the cavernous sinuses and posterior clinoid processes were left intact as there was involvement with and strong adhesion to internal carotid arteries. Pathological diagnosis was confirmed as giant cell tumor [Figure 2]. Postoperatively, bilateral abducens nerve palsy improved due to what seemed to be reduction of the physical distortion because of the reduced volume of the tumor, and a wait and scan policy was chosen according to the wishes of the patient and his guardian. However, denosumab therapy was initiated 3 months after the operation, because rapid regrowth of residual tumor was confirmed on MRI [Figure 1c]. Thereafter, tumor reduction and bone formation were induced [Figure 1d] and sustained for 5 years. Subtle changes of an ossified lesion under denosumab treatment could be clearly detected on CT images [Figure 3].

Denosumab treatment consisted of 120 mg subcutaneous injections every 28 days for the first 2 years, with additional doses on days 8 and 15 [Figure 3b]. Subsequently, the dosing interval was gradually prolonged to avoid the occurrence of side effects, with 4 monthly dosing for the next 1 year [Figure 3c], followed by a 6 monthly dosing for 2 years [Figure 3d and e]. With the extension of the dosing interval, there has been slight growth of ossified tumor, but it could be controlled to be within an acceptable range [Figure 3b-d]. Because the lesion has remained unchanged over the 1 year treatment by a 6 monthly dosing [Figure 3e], the treatment continues to be maintained at this dosing interval. The denosumab treatment has been well tolerated by the patient, and there have been no adverse effects with respect to the adjustment of the dosing interval.

DISCUSSION

Although complete removal with invaded bone is the preferred treatment for GCTB,[7,14,15] the extent of surgery can occasionally be limited due to proximity to critical structures, especially in skull base lesions as in the current case. Furthermore, GCTB, which is classified as benign, can grow locally aggressive with a high recurrence rate (up to 60%), especially after partial resection.[14-16] Therefore, the establishment of efficacious and safe adjuvant treatments for residual tumor may be the highest priority for long-term management of unresectable skull base GCTB.

Radiotherapy is not promising for the management of GCTB. Although there are some reports describing tolerable controllability of radiotherapy in managing GCTB,[7,15,16] a considerable number of reports have described its ineffectiveness or a high recurrence rate.[1,5] Moreover, radiotherapy can be associated with long-term morbidities, especially in young patients such as the current case. Likewise, skull base GCTB tends to be adjacent to and occasionally involve critical structures, such as the optic nerve and pituitary gland, which are vulnerable to radiation. Even worse, the possibility of radiation-induced malignant transformation of GCTB has also been conjectured.[4,6]

GCTB has exhibited resistance to most conventional chemotherapeutic agents, including interferons, ifosfamide, doxorubicin, cyclophosphamide, cisplatin, and other like treatments.[14] In a small retrospective series, the effectiveness of bisphosphonates for stabilization of local and metastatic lesions of GCTB has been reported.[15] In a nonrandomized prospective Phase II trial, however, adjuvant bisphosphonate

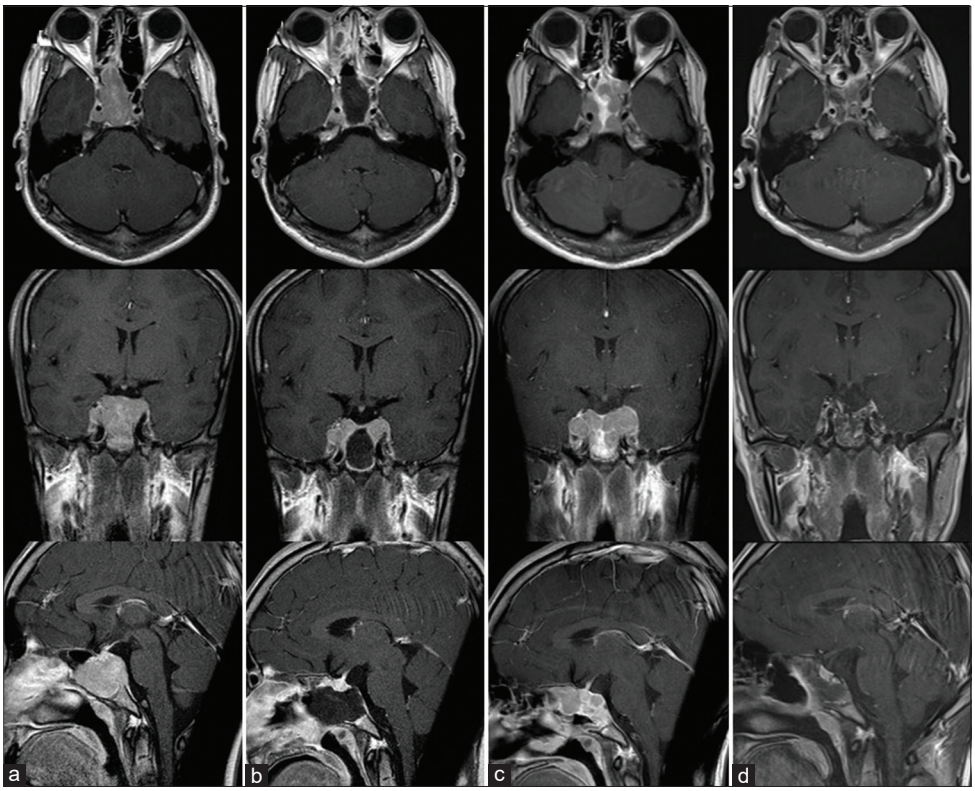

Figure 1: Axial, coronal, and sagittal views of gadolinium-enhanced T1-weighted MRI of a patient with giant cell tumor of sphenoid bone at preoperative (a), postoperative (b), 3 months after the operation (c), and 3 months after the initiation of denosumab treatment (d).

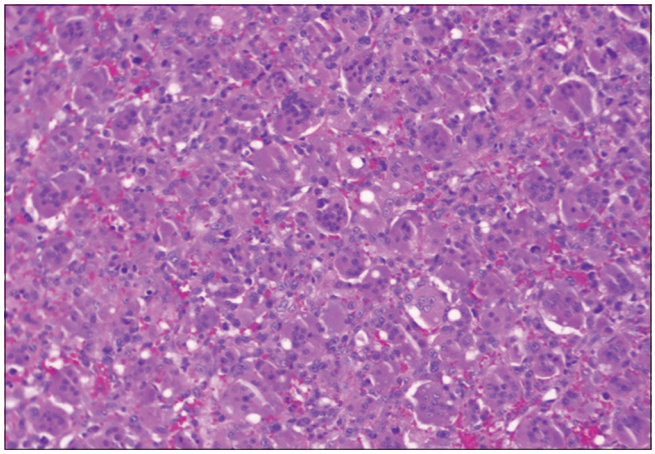

Figure 2: Photomicrograph of hematoxylin and eosin (H and E)-stained histopathologic specimens from a patient with a giant cell tumor of sphenoid bone, demonstrating numerous multinucleated osteoclast-like giant cells distributed diffusely among a background of neoplastic mononuclear stromal cells and mononuclear macrophage linage cells.

(zoledronic acid) was unable to demonstrate a lower recurrence rate after curettage.[8] Furthermore, other reports have challenged the efficacy of bisphosphonates as adjuvant in the management of unresectable GCTB.[12]

Denosumab has been establishing a firm position in the management of unresectable GCTB.[1,3,13-16] It remains unclear, however, how long treatment must or can continue. It is certain that lifelong treatment may not be the ideal therapeutic option, because it has been demonstrated that denosumab can cause some side effects, including hypocalcemia, hypophosphatemia, increased bone mineral density, and increased risk of fracture and osteonecrosis.[3,13] Thus, reducing the dose or extending the dosing interval as much as possible is desirable for patients who are unable to discontinue the medication. Based on this premise, we gradually extended the dosing interval of denosumab up to 6 monthly after achieving stabilization of the disease in the current case. Consequently, the lesion in the sphenoid bone, which was ossified and inhibited growth, has grown slightly but within an allowable range. This finding corresponded with results of *in vitro* studies that have shown denosumab not to work through cytotoxic effect on GCTB and the possibility of recurrence after the withdrawal of the drug.[10,15] Accordingly, it was considered that further extension of the dosing interval of the drug would be inappropriate in the current case. In the treatment of postmenopausal women with osteoporosis, it has been confirmed that denosumab treatment, with a dosage of 60 mg every 6 months for up to 10 years, is associated with low rates of adverse events, including

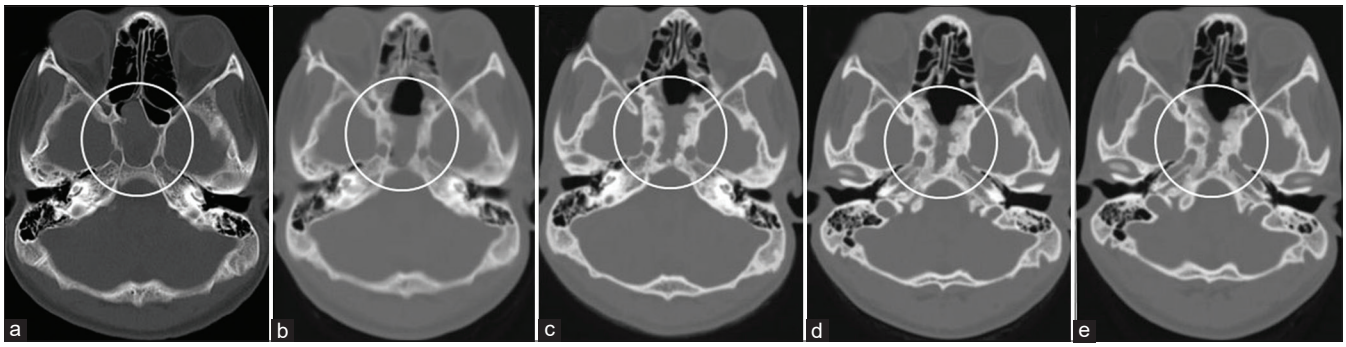

Figure 3: CT scans at preoperative (a), 2 years after the initiation of the denosumab treatment (b), a year after extending the dosing interval of denosumab to 4 monthly (c), and a year (d) and 2 years (e) after extending the dosing interval of denosumab to 6 monthly.

atypical femoral fracture (0.04%) and osteonecrosis of the jaw (0.3%).[2] Taken together, it was considered that the optimal extended dosing interval of denosumab treatment for GCTB after achieving the stabilization of the disease would be 6 monthly and that dosage reduction would be preferred if possible. For adjustment of the dosing interval, gradual extension seems to be recommended, as in the current case, because abrupt discontinuation of denosumab could cause excess osteoclast activity as a rebounding effect.[15]

CONCLUSION

Denosumab treatment was very useful as an adjuvant for unresectable GCTB in the skull base, as reported in the literature. It was considered that discontinuation of denosumab treatment for unresectable GCTB would be impossible due to the nature of the drug and that an adjustment of dosage or dosing interval according to each case after achieving the stabilization of the disease is both possible and important with long-term continuation of the drug, to avoid the occurrence of adverse effects. Extending the dosing interval up to 6 monthly, as could be done safely in the current case, can be considered a useful and appropriate measure.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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